Neurologic Aspects of Cardiac Emergencies

Lauren Ng, MD, MPH[a,b], Jing Wang, PhD[c], Laith Altaweel, MD[d], M. Kamran Athar, MD[b,e,*]

KEYWORDS

• Cardiac emergencies • Neurologic complications • Stroke • Acute brain injury

KEY POINTS

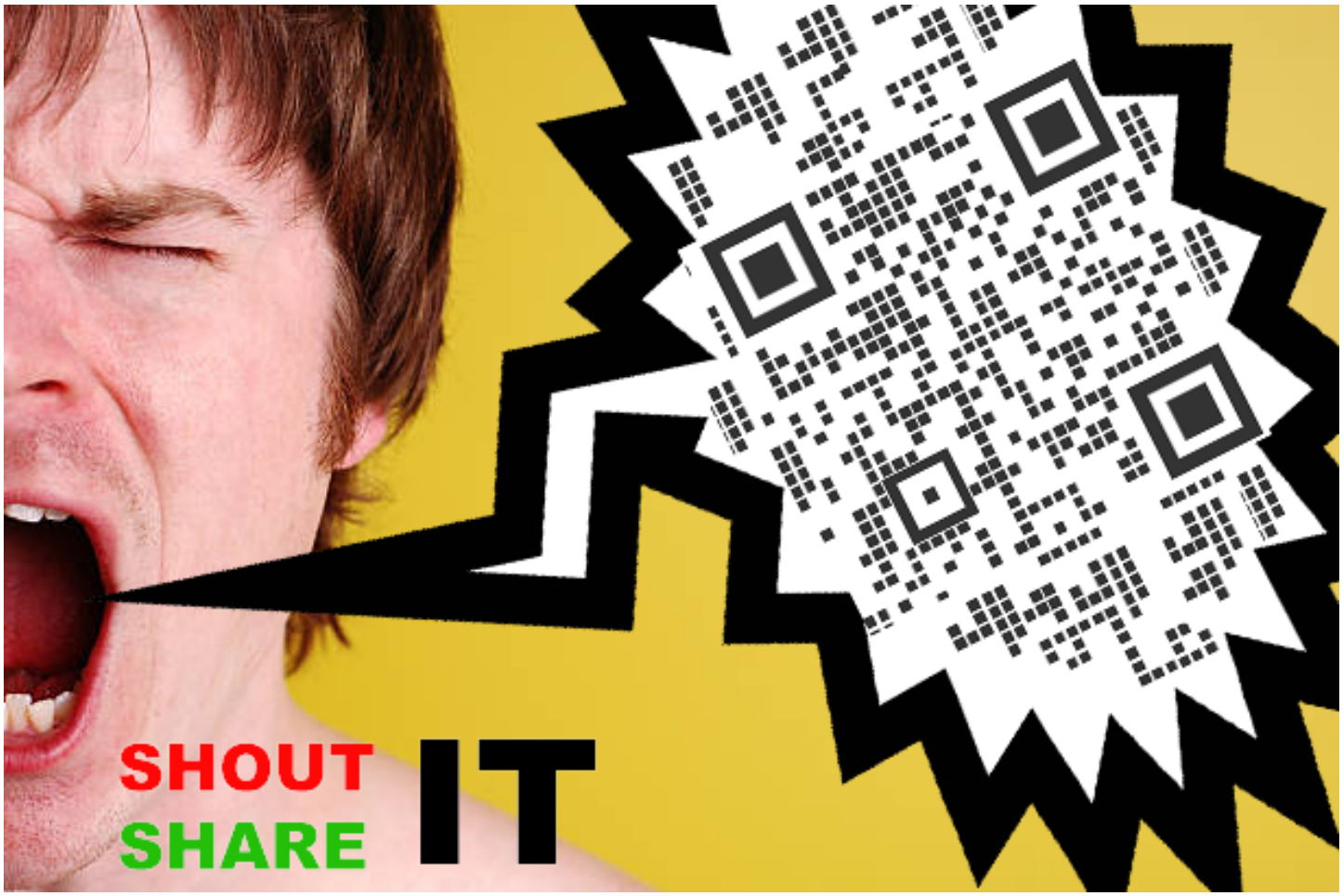
- Therapeutic hypothermia has improved neurologic outcomes after cardiac arrest, with newer prognostication models emerging.
- Hemorrhagic and ischemic stroke and transient ischemic attack are the most common neurologic complications associated with aortic dissection, ventricular assist devices and coronary artery bypass grafting.
- Neurologic complications occur in 20–40% of cases of infective endocarditis and include stroke, intracerebral hemorrhage, meningitis, brain abscess and intracranial mycotic aneurysms.
- There is a lack of data on the management of aortic dissection, ventricular assist devices, coronary artery bypass grafting and infective endocarditis in the setting of neurologic complications.
- Neurogenic stunned myocardium is an important disease entity that can mimic an acute myocardial infarction, but is a stress cardiomyopathy related to neurologic illness.

INTRODUCTION

Cardiac emergencies can be associated with a wide variety of neurologic complications and sequelae. These sequelae can be the most important factor in determining patient outcomes, including long-term functional outcomes. In this review, the important topic of cardiac arrest are discussed, with a focus on neuroprognostication and

[a] Division of Critical Care and Neurotrauma and Cerebrovascular Diseases, Department of Neurology, Thomas Jefferson University, 901 Walnut Street, 4th Floor, Philadelphia, PA 19107, USA; [b] Division of Critical Care and Neurotrauma, Department of Neurological Surgery, Thomas Jefferson University, 901 Walnut Street, 3rd Floor, Philadelphia, PA 19107, USA; [c] Department of Medicine, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22042, USA; [d] Neuroscience Intensive Care, Department of Medicine, Inova Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22042, USA; [e] Department of Medicine, Jefferson College of Medicine, Thomas Jefferson University, 1025 Walnut Street, Philadelphia, PA 19107, USA
* Corresponding author. Division of Critical Care and Neurotrauma, Departments of Neurological Surgery and Medicine, Jefferson College of Medicine, Thomas Jefferson University, 901 Walnut Street, 3rd Floor, Philadelphia, PA 19107.
E-mail address: Muhammad.athar@jefferson.edu

Crit Care Clin 30 (2014) 557–584
http://dx.doi.org/10.1016/j.ccc.2014.03.002 **criticalcare.theclinics.com**
0749-0704/14/$ – see front matter © 2014 Elsevier Inc. All rights reserved.


SHOUT
SHARE
IT

the emerging data, with regard to identifying more accurate predictors of neurologic outcomes in the era of therapeutic hypothermia (TH). Some of the recent controversies with regard to targeted temperature management in comatose survivors of cardiac arrest are also discussed. The next section focuses on neurologic complications associated with surgical disease and procedures, namely aortic dissection, infective endocarditis (IE), left ventricular (LV) assist devices (LVADs), and coronary artery bypass grafting (CABG). We believed that these topics should be discussed given the complexities in their management. In the final section of the review, the cause, pathogenesis, and management of neurogenic stunned myocardium (NSM), an important clinical entity, are discussed.

ANOXIC-ISCHEMIC ENCEPHALOPATHY

Epidemiology

About 450,000 Americans have cardiac arrest (CA) annually.[1] Eighty percent of CAs occur at home, and mortality for such arrests is more than 90%.[1,2] More than half the survivors have permanent brain damage of varying degrees.[3,4] The outcomes for in-hospital arrests are better, with restoration of spontaneous circulation in 44% of patients and survival to discharge in 17% of patients. Survivors of CA who remain comatose are presumed to have anoxic-ischemic encephalopathy. A wide range of neurologic outcomes is possible in such patients, ranging from brain death to good recovery.

Neuroprognostication and Predictors of Poor Outcome

The American Academy of Neurology has identified several predictors of poor neurologic outcome to assist with prognostication.[5] These predictors include absent pupillary or corneal reflexes at day 3 after CA, absent or extensor motor responses at day 3,[6–8] bilateral absent N20 responses of somatosensory evoked potentials on days 1 to 3,[9–12] serum neuron-specific enolase (NSE) greater than 33 ng/mL at days 1 to 3,[7,13] and the presence of myoclonus status epilepticus within 24 hours.[7,14]

In prospective studies involving 491 patients,[6,15–19] all 108 patients who had absent pupillary light reflex (PLR) at day 3 after CA had poor outcomes. Absent corneal reflex at 72 hours was shown to be associated with poor outcomes in 2 prospective studies.[6,7] In another prospective study of 407 patients, myoclonic status epilepticus at 24 hours after CA was associated with no false-positive results for poor outcomes (95% confidence interval [CI], 0–14).[7] Several prospective studies have shown that a motor response to noxious stimuli that was no better than extensor posturing at 72 hours was associated with poor outcome.[6,7,16] However, these indicators of poor prognosis are derived from patients not treated with TH.

Several recent studies have looked into the accuracy of these predictors in the era of TH after CA. Fugate and colleagues[20] found that absent PLR, absent corneal reflexes, and motor response no better than extensor at day 3 remained predictive of a poor outcome in patients who received TH. Similarly, absent N20 responses were still predictive of poor outcome. However, an increased NSE level measured 1 to 3 days after CA was a less reliable predictor of poor outcome in such patients. However, pharmacologic sedation related to TH may influence prognostication of neurologic outcomes after CA. Recovery of motor responses, especially, may be delayed. A small study of 37 patients[21] showed that 2 of 14 patients who had a motor response no better than extensor posturing on day 3 showed some recovery of consciousness on day 6. **Table 1** compares the predictors of poor outcome both before and after the era of TH.

More recently, Oddo and Rossetti[22] adopted a multimodal approach for outcome prediction after CA and TH. These investigators found that clinical examination, which

Table 1
Predictors of poor outcome after CA

Before TH	After TH
Absent PLR	Absent PLR
Absent corneal reflexes	Absent corneal reflexes
Motor response no better than extensor	Motor response no better than extensor[a]
Absent N20 response	Absent N20 responses[a]
Myoclonic status epilepticus	Serum NSE >33 ng/mL[a]
Serum NSE >33 ng/mL	

[a] Data on these responses remain controversial.

included incomplete recovery of brainstem reflexes and myoclonus, nonreactive hypothermic electroencephalography and serum NSE levels greater than 33 μg/L were independent predictors of poor outcome in comatose patients after CA and the combination of the 3 had the highest specificity (100%) and positive predictive value for poor outcome.

Hypothermia After CA

TH affects multiple pathways involved in ischemia-reperfusion injury after CA, and neurologic outcomes after CA have improved with the introduction of TH. Two major studies changed clinical practice in the management of out-of-hospital CA. The first study led by Bernard,[23] was performed in Australia between 1996 and 1999 on patients presenting with ventricular fibrillation (VF) and return of spontaneous circulation (ROSC) with persistent coma. Randomization occurred in the field, and a total of 84 patients were enrolled. Patients in the hypothermia arm were cooled to 33°C beginning in the field with ice bags. In the multivariate analysis, the odds ratio (OR) for a good outcome (defined as survival to hospital discharge to either home or a rehabilitation facility) in the hypothermia group compared with the normothermia group was 5.75 (CI 1.47–18.76; $P = .011$). The difference in mortality in the 2 groups was not significant.

The second study was completed by the Hypothermia After Cardiac Arrest Study Group.[24] This study enrolled patients in the emergency department who had witnessed CA caused by VF or pulseless ventricular tachycardia (VT) with ROSC within 60 minutes and no response to verbal commands. Two hundred and seventy-five patients were enrolled, and in the hypothermia arm, patients were cooled to 32°C to 34°C using an external cooling device as well as ice packs. The primary outcome was a favorable neurologic outcome at 6 months using the Pittsburgh cerebral performance category (**Table 2**) of 1 or 2 of 5. Patients were not randomized well in this study, but

Table 2
Pittsburgh Cerebral Performance Category Scale

CPC 1	None to mild disability, able to work, may have mild neurologic or psychological deficit
CPC 2	Moderate disability, able to complete independent activities of daily life and work in a sheltered environment
CPC 3	Severe disability, dependent on daily support. Ranges from ambulatory to severe dementia to paralysis
CPC 4	Coma or vegetative state
CPC 5	Brain death

the rate of favorable neurologic outcome and mortality at 6 months were improved. There was no statistical difference in rate of complications in either group, although there was a trend toward increased rates of infection in the hypothermia arm.

TH is routinely performed in patients who present with CA and ROSC, given its neuroprotective effects. A prospective study looked at the cognitive outcomes of patients undergoing hypothermia after CA[25] and reported that 79% of patients who were working at the time of CA returned to work. This study supports the view that those who survive are likely to have a good outcome.

Although these studies support the use of TH, a recent study conducted by the Targeted Temperature Management Trial Investigators[26] that compared targeted temperature management of 33°C with 36°C after CA showed no difference in outcome. In this study, 75% of patients had VT or VF arrest, and 25% presented with pulseless electrical activity. This finding is in contrast to previous studies in which all patients had VT/VF arrest. The study suggests that controlled normothermia and fever control are what confer outcome benefit and that maintaining temperatures of 36°C after CA is all that is needed. Additional studies need to be performed before there is a change in practice.

Despite advances in emergency services and advanced cardiac life support, survival from CA remains low. For comatose survivors of CA, chances of long-term survival without significant neurologic deficits also remain low. Predicting neurologic outcomes after CA is challenging. Several variables of poor neurologic outcome have been identified. There is emerging evidence that in the era of TH, a multimodal approach incorporating clinical examination, electrophysiologic variables, and serologic data may be more beneficial in accurately predicting neurologic outcomes in comatose survivors of CA treated with TH. In addition, there is no doubt that temperature control in the period immediately after CA and prevention of hyperthermia is important to improve outcomes. Whether normothermia confers the same benefit as induced hypothermia is open to debate.

SURGICAL DISEASE

Neurologic Complications After Aortic Dissection

Introduction

Stroke is the most common neurologic complication of aortic dissection, and is the initial presenting symptom in 5% to 29% of cases, mainly resulting from supra-aortic arch involvement.[27–31] Often, the diagnosis of aortic dissection is missed in patients who present with stroke, because only two-thirds of patients presenting with neurologic symptoms had any chest or back pain, whereas 94.4% of patients without neurologic symptoms experienced pain.[27,28] In 1 study, the average mean National Institutes of Health Stroke Scale (NIHSS) (**Table 3**) on admission was 12.9.[29] Right hemispheric strokes are more common, with an incidence of 69.2% to 81%, compared with 13% for left hemispheric strokes and 6% for bilateral strokes.[27,29] Other neurologic symptoms reported with aortic dissection are listed in **Box 1**.[27,30,32] These symptoms are believed to result from either extension of the dissection flap and occlusion of the true lumen or hypoperfusion syndromes as a result of hypotension and shock.[27,30] In patients who underwent surgery, 47.5% had postoperative neurologic complications, with stroke being the most common diagnosis.

Aortic dissection repair and neurologic outcomes

Optimal treatment of aortic arch dissection in patients with neurologic deficits is not clear. Patients with ascending aortic dissection who present with stroke and coma are less likely to go to surgery and have higher hospital mortality.[28] Multiple studies

Table 3
NIHSS

Item	Points	Description
1a. LOC	0	Alert
	1	Drowsy
	2	Obtunded
	3	Coma
1b. LOC questions	0	Answers both questions correctly
	1	Answers 1 question correctly
	2	Answers neither question correctly
1c. LOC commands	0	Performs both tasks correctly
	1	Performs 1 task correctly
	2	Performs neither task correctly
2. Best gaze	0	Normal horizontal movements
	1	Partial gaze palsy
	2	Compete gaze palsy
3. Visual field	0	No visual field defect
	1	Partial hemianopia
	2	Complete hemianopia
	3	Bilateral hemianopia
4. Facial movement	0	Normal
	1	Minor facial weakness
	2	Partial facial weakness
	3	Complete unilateral palsy
5. Arm motor function	0	No drift
a. Left	1	Drifts before 5 s
b. Right	2	Falls before 10 s
	3	No effort against gravity
	4	No movement
6. Leg motor function	0	No drift
a. Left	1	Drifts before 5 s
b. Right	2	Falls down before 5 s
	3	No effort against gravity
	4	No movement
7. Limb ataxia	0	Absent
	1	Present in 1 limb
	2	Present in 2 limbs
8. Sensory	0	No sensory loss
	1	Mild to moderate sensory loss
	2	Severe to total sensory loss
9. Best language	0	Normal
	1	Mild aphasia
	2	Severe aphasia
	3	Mute or global aphasia
10. Articulation	0	Normal
	1	Mild to moderate dysarthria
	2	Severe dysarthria
11. Extinction and inattention	0	No abnormality
	1	Mild loss of 1 sensory modality
	2	Severe loss of 2 modalities

Abbreviation: LOC, level of consciousness.

Box 1
Neurologic symptoms in aortic dissection

- Stroke
- Spinal ischemia
- Ischemic neuropathy
- Hypoxic encephalopathy
- Syncope
- Tonic-clonic seizures
- Somnolence
- Coma
- Transient global amnesia

have looked into the safety of surgery and risk factors for transient neurologic dysfunction (TND) and permanent neurologic dysfunction (PND). In a retrospective study of 1873 patients,[28] 100% of patients with coma and 76.2% with stroke died with medical management alone. In the surgical arm, mortality decreased to 44% in those with preoperative coma and 27% in patients with stroke. There was postoperative improvement in symptoms in 74.2% of patients with coma and 80.4% with stroke. This study concluded that surgery was protective against mortality in patients with preoperative brain injury and a reversal of the injury can occur with surgery. These findings are supported by the German Registry for Acute Aortic Dissection Type A, which found that 62.1% of those with preoperative neurologic dysfunction had resolution of symptoms after surgery, with hemiparesis resolving in 70.5%, paraparesis in 78.8%, aphasias in 80.6%, and coma in 70.9%.[33]

In addition, spinal cord injury (SCI) is an important complication of thoracic aortic aneurysm repair, complicating 20% of open repair and 3.88% of thoracic endovascular aortic repair (TEVAR).[34] Three randomized control trials[35–37] have suggested that prophylactic cerebrospinal fluid (CSF) drainage reduces the risk of perioperative SCI in open repair of thoracic aortic aneurysms. However, in the setting of TEVAR, there have been conflicting data on the use of prophylactic CSF drainage. In a recent systematic review,[34] SCI after routine prophylactic drainage was 3.2% compared with 3.47% in patients without routine prophylactic drainage and 5.60% in patients with selective prophylactic drainage; however, there was evidence of bias in the selective drainage group. Thus, although prophylactic CSF drainage can be recommended in patients undergoing open repair, more research needs to be undertaken on the use of prophylactic drainage in TEVAR.

Predictors of neurologic outcome after aortic surgery

Baseline NIHSS and time to surgery seem to be the most important predictors of neurologic improvement postoperatively. In a retrospective study of 41 patients,[38] recovery was seen in 88% of patients with NIHSS less than 11% and 85% if the time to surgery was less than 9.1 hours. In a subgroup analysis[38] combining the 2 risk factors for poor outcome (NIHSS >11 and time to surgery >9.1 hours), recovery was 100% in patients with no risk factors, 75% in patients with 1 risk factor, and 0% in those with both risk factors. This finding is consistent with the results by Estrera and colleagues,[29] in which 80% of patients who underwent surgery in less than 10 hours had neurologic improvement, in contrast to no improvement in symptoms for those operated on after 10 hours.

Other factors that have been identified to imply poor neurologic recovery are preoperative cerebral malperfusion syndrome, use of deep hypothermic circulatory arrest, and duration of cardiopulmonary bypass (CPB) and circulatory arrest.[33,39,40] No single surgical cerebral protection strategy has proved to be superior to another. An increase in mortality has been noted if bypass was performed for greater than 30 minutes without the use of anterior cerebral perfusion and greater than 60 minutes if cerebral perfusion was used.[41]

In patients without previous neurologic deficits, factors associated with TND and PND include poor preoperative mental status, male gender, diabetes and peripheral artery disease, EuroSCORE, aortic cross-clamp time, and femoral cannulation.[42] Data regarding the effect of age on neurologic dysfunction are variable; some studies show age as a risk factor, whereas others do not.[40,43]

Overall, stroke is a common presenting symptom of aortic dissection and must be recognized immediately. Current literature seems to support early surgery in patients with neurologic dysfunction, but this warrants further study. Risk factors for the development of neurologic dysfunction after aortic dissection repair include preoperative cerebral malperfusion syndrome, duration of CPB, circulatory arrest, time to surgery, and baseline NIHSS score (**Box 2**).

Neurologic Complications of Ventricular Assist Devices

Stroke and transient ischemic attack

Stroke and transient ischemic attacks (TIAs) are the most common neurologic complications after placement of a ventricular assist device, with incidence ranging from 2.7% to 48% of patients.[44–47] Other neurologic events that have been described include air embolism, seizures, brain abscess, metabolic encephalopathy, bilateral tremors, dementia, and anoxic brain injury secondary to CA.[48–50] In many cases, there were multiple events per patient. The time course of neurologic complications after LVAD placement is variable, with events occurring from 3 to 368 days after implantation. In most studies, the highest incidence is within 30 days of placement.[49,51,52] Patients with early complications occurring less than 14 days after implantation had 67% mortality, and 1 study reported stroke as cause of death in 8% of patients.[53,54]

Pathogenesis and risk factors

Thromboembolism is the leading cause of neurologic events.[44,49,53] Emboli are believed to emanate from the pump itself, with deposits found on the inflow valves in explanted devices, although LV thrombus and heart valves can contribute.[44,55] It is postulated that the ventricular assist devices alter the coagulation and fibrinolytic

Box 2
Risk factors for neurologic dysfunction after aortic dissection repair

- Baseline NIHSS greater than 11
- Time to surgery greater than 10 hours
- Preoperative malperfusion syndrome
- Use of deep hypothermic circulatory arrest
- Duration of CPB and CA
- History of diabetes
- Male gender
- Peripheral artery disease

systems, leading to increased platelet, coagulant, and fibrinolytic activities (Fig. 1).[44,56,57] This finding is secondary to foreign and irregular surfaces on the device, which lead to turbulent blood flow and shear stress, resulting in hypercoagulability, stasis, and device-related infection.[49] Infection has been associated with increased risk of neurologic complications and is believed to cause changes in the microvascular structure and reactivity, leading to coagulation abnormalities.[58] Other risk factors for postoperative stroke are listed in **Box 3**.[45,53,58]

The rates of neurologic complications differ based on the device implanted, with the HeartMate (Thoratec Corp, Pleasanton, CA, USA) device having a lower incidence of stroke compared with ThoratecBiVAD (Thoratec Corp, Pleasanton, CA, USA), Thoratec LVAD (Thoratec Corp, Pleasanton, CA, USA), and Novacor (WorldHeart, Oakland, CA, USA), with 75%, 64%, 63%, and 33% freedom from stroke at 6 months, respectively.[51] This situation is possibly caused by the biointimal surface on the HeartMate, which reduces the risk of thromboembolism.[44] However, the HeartMateII (Thoratec Corp, Pleasanton, CA, USA) has seen a sharp increase in the rate of thrombosis since 2011 occurring about 1 month after implantation, and it is unknown what the inciting factor is.[55]

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is also a complication with LVAD, given the concomitant use of both anticoagulants and antiplatelet therapy.[59,60] However, there is little in the literature on how to manage these patients. The largest study included 330 patients with an LVAD, of whom 36 (11%) had ICH (defined as subarachnoid, subdural, or intraparenchymal hemorrhage).[60] All patients were on warfarin and aspirin at the time of presentation, with a mean international normalized ratio of 1.6, although

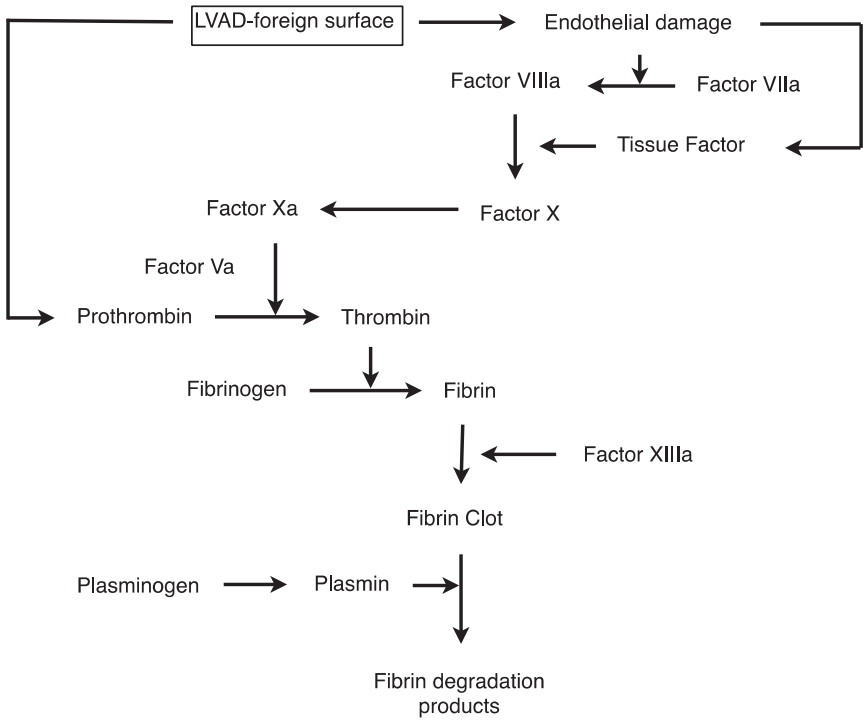


Fig. 1. Mechanism of thrombus formation in LVAD.

Box 3
Risk factors for stroke after LVAD implantation

- Infection
- Subtherapeutic international normalized ratio
- Atrial fibrillation
- Heparin-induced thrombocytopenia
- Baseline cardiomyopathy
- Higher mean right atrial pressure preoperatively
- Lower total protein after surgery
- Larger right ventricular end-diastolic dimension preoperatively
- History of stroke
- INTERMACS profile of 1 or 2

patients presenting with subarachnoid or subdural hemorrhage also had a history of fall or trauma.[60] In general, those with intraparenchymal hemorrhage as well as low Glasgow Coma Scale score had higher mortality and morbidity than those presenting with subarachnoid hemorrhage (SAH) or subdural hematoma.[60] Aspirin and warfarin were both stopped for a median time of 6 days and 10.5 days, respectively, in these patients, with no pump failure or ischemic events observed and no delayed rehemorrhage when resumed.[60] This study suggests that withholding aspirin for about a week and warfarin for about 10 days was adequate to prevent rehemorrhage as well as prevent pump failure and ischemic events.[60] Given the limited data, more studies are needed in this area.

Stroke and TIA are the most common neurologic complications after ventricular assist device placement and are mainly thromboembolic in nature. Major risk factors for neurologic complications include the type of device implanted, infection, and subtherapeutic anticoagulation.

Neurologic Complications of IE

Incidence

IE remains a major clinical problem, with mortality of 20% to 40%.[61,62] Neurologic complications occur in about 20% to 40% of cases of IE during the active course of the disease.[61,63] In ICE-PCS (International Collaboration on Endocarditis-Prospective Cohort Study),[62] the incidence of stroke was 17%. Sonneville and colleagues[64] found a 55% incidence of neurologic events among 198 patients with IE admitted to the intensive care unit (ICU).

Risk Factors

Several risk factors have been found to influence the occurrence of neurologic complications in IE (**Box 4**). Risk of cerebral embolism (CE) is higher with mitral valve disease and is maximal when vegetations involve the anterior mitral valve leaflet.[65] Vegetations greater than 10 to 15 mm and mobile vegetations are also associated with an increased risk of CE.[65–67] In a prospective study of 384 patients who underwent transesophageal echocardiography, size of the vegetation (10 mm) and its mobility were independent predictors of CE. Frequency of neurologic complications is 2 to 3 times more with *Staphylococcus aureus* infection than with other pathogens.[63,68] In some studies, it has been identified as the most important risk factor

Box 4
Risk factors for neurologic complications in IE

- Mitral valve vegetation, particularly anterior mitral valve leaflet
- Vegetations greater than 10 to 15 mm
- Mobile vegetations
- *Staphylococcus aureus* infection

for neurologic complications.[68] However, despite adequate antibiotic therapy, new embolic events are still observed in about 7% of cases.[69] If anticoagulant treatment is necessary, it is particularly associated with ICH.[68]

Complications

Ischemic events

Stroke or TIAs account for 40% to 60% of neurologic complications of IE[68] and result from dislodgement or fragmentation of endocardial vegetations. In addition, clinically silent CE is increasingly being reported and may be detected in up to 30% of patients with left-sided endocarditis using repeated brain magnetic resonance imaging.[70] However, the clinical importance of silent CE is unclear.

ICH

ICH complicates about 5% of cases of IE.[64,71–74] Mechanisms include hemorrhagic transformation of septic embolic infarcts, rupture of intracranial mycotic aneurysms (ICMAs), and erosion of arterial wall with subsequent hemorrhage. Erosion of arterial wall with subsequent hemorrhage is seen mostly in patients with *S aureus* IE. Risk factors for ICH include anticoagulant treatment, *S aureus* infection, and severe thrombocytopenia.[75]

Meningitis

Meningitis occurs in 2% to 20% of patients with IE. It results from dissemination of emboli into meningeal vessels. In most case series, it is diagnosed by presence of CSF pleocytosis with or without isolation of causative microorganism on culture.

Brain abscess

Brain abscess is a rare complication of IE, occurring in less than 5% of patients with IE. Garcia-Cabrera and colleagues[68] found 2 cases of brain abscess in a cohort of 1345 patients with IE. In the critically ill, it was observed in 14 (13%) of 108 patients with IE.[64] IE should be suspected in the absence of an obvious source of brain abscess and when multiple abscesses are present. *S aureus* is the most common pathogen for brain abscess in the setting of IE.

ICMAs

ICMAs account for 2% to 4% of neurologic complications of IE. The incidence is likely underestimated, because cerebral angiography is not performed regularly.[76] The pathologic mechanism of ICMA is from septic embolization to the vasa vasorum with destruction of the adventitia and the intima. ICMAs are multiple in 20% to 25% cases and are mostly located on the distal bifurcations of middle cerebral artery. Four-vessel cerebral angiography is the gold standard for diagnosis of ICMAs. However, magnetic resonance angiography has high sensitivity (90%–95%) and is especially useful for follow-up.[76]

Serial imaging can be used to follow small or unruptured ICMAs, because most resolve with antibiotic therapy. Treatment options for ruptured ICMAs or aneurysms

that are enlarging or persistent despite appropriate antimicrobial therapy include endovascular coiling or surgical clipping.

Most neurologic complications occur before or during the first week of treatment. Once appropriate antimicrobial therapy is started, the incidence gradually decreases during the following weeks. In ICE-PCS,[77] the crude incidence of stroke decreased from 4.82/1000 patient days in the first week of therapy to 1.71/1000 patient days in the second week of treatment. This rate continued to decline with additional therapy.

The decrease in the rate of neurologic complications after a week of treatment was less pronounced when vegetations were greater than 1 cm in diameter.[59] In cases of vegetations greater than 3 cm, risk of embolic events remained high (20%). This is an important consideration when deciding on timing of cardiac surgery.

Impact of Neurologic Complications on Outcomes

Overall mortality for IE ranges from 20% to 40%.[62,78–81] Functional outcomes have also been evaluated in small observational studies. Sonneville and colleagues[64] found that only 31 of 106 patients in the ICU with IE and neurologic complications had a modified Rankin Scale lower than 3 at follow-up (3.9 months [3–8.5]) (**Table 4**). In another cohort of 68 patients,[82] full neurologic recovery was observed in 78% of patients with NIHSS at admission of 4 to 9 but in only 33% when the score was greater than 15.

Timing of Cardiac Surgery

The indications for surgery are listed in **Box 5**. The timing of valvular surgery in case of IE complicated by stroke is controversial, because of concern regarding the safety of CPB in patients with stroke. Anticoagulation during cardiac surgery may increase the risk of hemorrhage after cerebral infarction. Hypercoagulability or hypotension during CPB may exacerbate preexisting ischemic brain lesions. Earlier studies[82–84] have reported high rates of postoperative morbidity and mortality. However, more recent studies[85,86] have suggested better outcomes of patients with IE with stroke who underwent cardiac surgery, particularly in the presence of ischemic rather than hemorrhagic stroke.

Piper and colleagues[85] found the risk of neurologic deterioration to be low when surgery was performed within 72 hours. Barsic and colleagues[86] showed that in patients with IE and ischemic stroke, there was a nonsignificant trend toward increased

Table 4
Modified Rankin Scale

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Adapted from Van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–7.

Box 5
Indications for surgery in IE

- Hemodynamic failure related to valve destruction
- Persistent fever despite appropriate antibiotic therapy
- Development of abscesses or fistulas caused by perivalvular spread of infection
- Highly resistant organisms (*Coxiella burnetii*, *Brucella*, aggressive staphylococcal strains, fungi)
- Prosthetic valve endocarditis, particularly in the early postoperative phase
- Large vegetations with high risk of embolism (10 mm and mobile)
- Vegetations with size increasing despite appropriate antibiotic therapy

in-hospital mortality in the early surgery (surgery within 1–7 days of an ischemic stroke) group. However, 1-year mortality was similar in both groups. This study excluded patients with hemorrhagic stroke.

Current recommendations, which are not based on prospective data, are to delay surgery for 2 to 4 weeks in the case of large cerebral infarction and for 4 weeks in the event of ICH, unless a delay in surgery puts the patient at immediate risk of death.[87–89]

Neurologic complications are common in patients with IE. Mitral valve disease, vegetations greater than 10 to 15 mm, and mobile vegetations are associated with the greatest risk of CE. The risk of embolism decreases gradually once antimicrobial therapy is initiated. Timing of cardiac surgery is controversial, although there is recent literature showing that early surgery may be performed safely in selected patients with ischemic stroke. In patients with hemorrhagic stroke, surgery is usually delayed for at least 4 weeks.

Neurologic Complications of CABG

Incidence

Neurologic events complicating CABG are varied, with stroke being an important cause of morbidity and mortality. These neurologic complications are listed in **Table 5**, using the classification from Roach and colleagues.[90] The incidence of stroke ranges from 0.9% to 16% of cases, with 30% to 60% of patients developing neuropsychological changes.[91–94] Studies have observed a 10-fold increase in in-hospital mortality in patients developing type I outcomes and a 5-fold increase in type II outcomes, as well as mortality ranging from 0% to 38% from stroke in patients with CABG with an increased length of ICU stay, hospital stay, and cost.[90,93–95]

Risk Factors

Several studies have focused on identifying risk factors for stroke after cardiac surgery, which are listed in **Box 6**.[90–93,95,96] Bucerius and colleagues[97] prospectively

Table 5
Neurologic complications of CABG

Type I	Type II
Death caused by stroke or hypoxic encephalopathy	New deterioration in intellectual function
Nonfatal stroke	Confusion
TIA	Agitation
Stupor or coma at discharge	Disorientation
	Memory deficit
	Seizure without focal injury

Box 6
Risk factors for neurologic events in CABG

- Age older than 60 years
- History of stroke or TIA
- Carotid bruits or carotid occlusion
- Peripheral vascular disease
- History of hypertension
- Pulmonary disease
- Ascending aortic disease
- Perioperative myocardial infarction
- Low LV ejection fraction
- Perioperative hypotension

evaluated the incidence and predictors of perioperative stroke among 16,184 consecutive adult patients undergoing cardiac surgery. The overall incidence of stroke was 4.6%, but varied according to procedure, with valvular surgery having the highest rate and beating heart CABG with the lowest incidence of stroke. In multivariate analysis,[97] independent risk factors for stroke included history of cerebrovascular disease, peripheral vascular disease, diabetes, hypertension, previous cardiac surgery, preoperative infection, urgent operation, CPB time more than 2 hours, need for intraoperative hemofiltration, and high transfusion requirement. In this analysis, a history of cerebrovascular disease was the strongest preoperative predictor of stroke. Redmond and colleagues[92] looked at patients with a history of stroke and observed a higher incidence of stroke, TND, depressed level of consciousness, confusion, longer time to awaken from anesthesia, longer to wean from mechanical ventilation, higher incidence of aspiration and reintubation, longer ICU stay, and higher mortality. This situation is believed to be caused by increased vulnerability and susceptibility to the effects of CPB in previously injured brain tissue.

Intraoperative Factors

Additional intraoperative factors that are associated with increased stroke risk are listed in **Box 7**.[94,96,98] Several studies have looked at off-pump CABG with CPB (OPCAB) versus conventional CABG with CPB (CCAB) to decrease the risk of stroke and neurocognitive outcomes. Although there is some evidence to suggest that OPCAB decreases the risk of stroke, mortality, and delirium in patients undergoing CABG, the data have been controversial.[99–102] In 2 studies, OPCAB was associated with fewer embolic phenomena as observed on intraoperative transcranial Doppler, but they had differing results with regard to neurocognitive testing.[103,104] One failed to show any difference in neurocognitive testing in the CCAB group, whereas the other showed better neurocognitive function at discharge, but this effect dissipated at 6 weeks and 6 months.[103,104]

Several randomized control trials Veterans Affairs Randomized On/Off Bypass, CABG Off or On Pump Revascularization Study, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (ROOBY, CORONARY, and GOPCABE) have failed to show any difference in morbidity or mortality, including stroke and neurocognitive function, at 30 days and 1 year.[105–108] However, these trials have inherent selection bias, either excluding many of the sicker or older patients or placing them in the

Box 7
Intraoperative risk factors for stroke in CABG

- Cold cardioplegia
- Intraoperative or postoperative IABP
- Duration on CPB
- Return to CPB after initial separation
- Extensive aortic manipulation
- Prolonged inotrope use
- Atrial fibrillation
- Low cardiac output syndrome
- Ventricular or atrial thrombus

CCAB group. Thus, the results of decreased mortality and complications may be a result of different patient populations as opposed to surgical modality. The ROOBY trial noted that enrolled patients had a significantly lower predicted risk of death than those who were excluded, and the GOPCABE Study Group also noted that excluded patients were more likely to have an ejection fraction (EF) less than 30% and to be in critical condition before surgery.[105,108] Thus, there is not enough strong evidence to suggest that OPCAB versus CCAB leads to decreased mortality, stroke, and delirium.

NSM

Synopsis

NSM resembling acute coronary syndrome or acute myocardial infarction (AMI) can occur in the setting of acute brain injury, predominantly in patients with poor grade aneurysmal SAH, namely Hunt Hess scale greater than 3 (**Table 6**).[109] Patients with SAH who developed NSM have substantially higher mortality and morbidity. Prompt recognition and early intervention of NSM in patients with SAH are key to improving clinical outcomes. The main aspects of managing NSM include treatment of underlying neurologic conditions, hemodynamic support with vasopressors, and supportive care.

Introduction

NSM is an acquired reversible LV cardiomyopathy in the absence of atherosclerotic coronary artery disease.[110,111] NSM is also known by several other names (**Box 8**),

Table 6
Hunt Hess Scale

Grade	Clinical Description
1	Asymptomatic or minimal headache and slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity, and vegetative disturbances
5	Deep coma, decerebrate rigidity, moribund

Adapted from Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968;28(1):14–20.

Box 8
Interchangeable nomenclature in the literature

- NSM
- Takotsubo cardiomyopathy
- Stress-induced cardiomyopathy
- Reversible LV dysfunction
- Transient apical ballooning
- Broken heart syndrome
- Ampulla cardiomyopathy

and is associated with numerous acute physical or psychological conditions (Box 9). The pathophysiology of NSM relates to excessive catecholamine release at the time of a stressor, which results in a clinical syndrome similar to an AMI. The syndrome presents with chest pain, electrocardiographic (EKG) abnormalities, increased troponin (TnI) levels, and abnormal echocardiogram. There are important distinguishing features, such as reversible regional wall motion abnormalities, which do not adhere to 1 coronary vascular territory. Yet, although NSM is reversible, it is associated with worse outcomes in brain-injured patients.

This discussion focuses on aneurysmal SAH. SAH is a condition that afflicts more than 30,000 Americans per year and is associated with significant morbidity and mortality. Clinically, the rupture of an aneurysm and extravasation of blood into the subarachnoid space results in sudden headache, syncope, and even death caused by the sudden increase of intracranial pressure (ICP). This acute stressor likely contributes to the pathogenesis of NSM. Early recognition and treatment by securing the aneurysm, either by coiling or clipping, CSF diversion, and management of increased ICP are critical to improving patient outcomes. Approximately 3 to 14 days after onset of SAH, up to one-third of patients develop delayed cerebral ischemia (DCI), or transient neurologic deficits or stroke, which further adversely affects morbidity and mortality. The treatment of DCI includes medical therapy such as intravenous fluid administration and blood

Box 9
Common neurologic conditions triggering NSM

- Aneurysmal SAH[2–5]
- ICH[6]
- Ischemic stroke
- Traumatic brain injury[5,7]
- Status epilepticus[7]
- Encephalitis[8,9]
- Acute myelitis[8,9]
- Guillain-Barré syndrome[10]
- Acute hydrocephalus and ventriculoperitoneal shunt malfunction[11–13]
- Reversible posterior leukoencephalopathy syndrome[14]
- Acute spinal cord infarction[14]
- Metastatic brain tumors[15]

pressure augmentation with vasopressors and, in certain cases, endovascular rescue therapy. The relationship among NSM, SAH, and DCI is discussed in this context.

PATHOGENESIS

The pathogenesis of NSM is still not fully understood but is believed to be related to excessive catecholamine release at the time of acute physical or psychological stress. Fig. 2 outlines a general pathway of cardiac injury. As shown in Fig. 2, acute stress results in stimulation or injury to autonomic centers of the brain, such as the right insular cortex, amygdale, and hypothalamus, resulting in excessive sympathetic outflow.[112–114] This situation leads to catecholamine release at the sympathetic nerve terminals that act on α and β receptors and Ca^{2+} channels on myocytes to induce excessive Ca^{2+} influx and production of oxidative free radicals,[115] culminating in reduced ventricular function. Other mechanisms contributing to cardiac injury include[116,117]: (1) coronary artery spasm; (2) coronary microvascular dysfunction; and (3) neuroinflammation. The combination of these mechanisms contributes to reduced cardiac function noted in NSM.

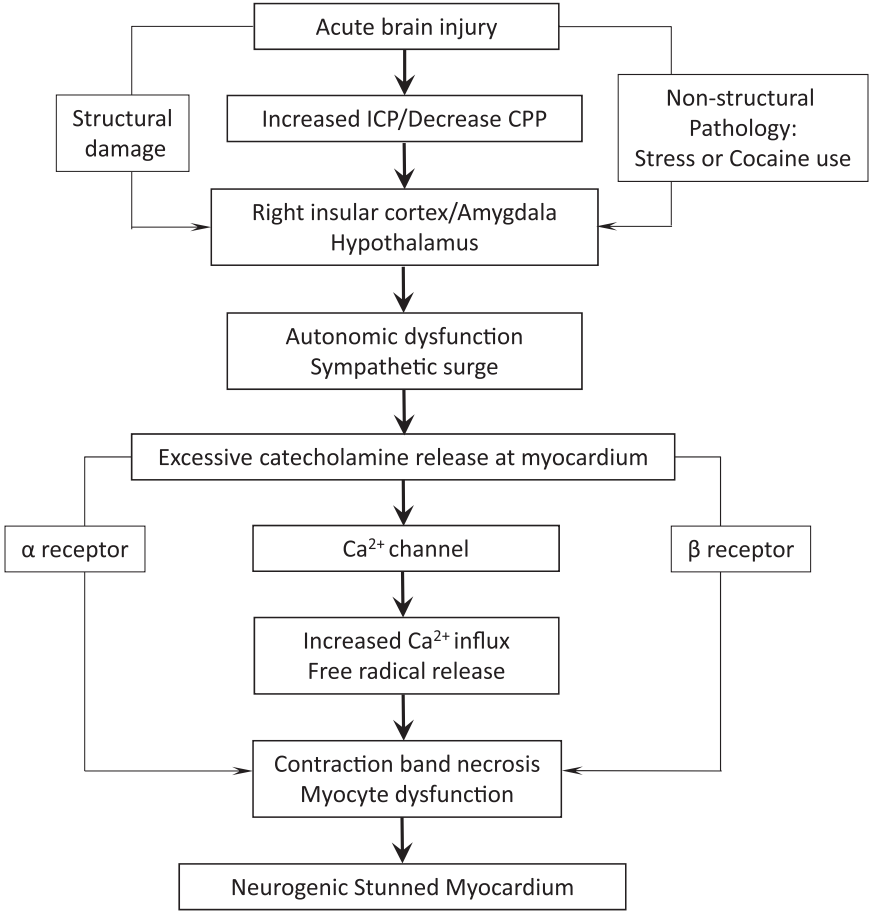


Fig. 2. Mechanism of NSM.

Incidence

The incidence of NSM is unclear, because most studies are retrospective. One prospective study found that 28% of patients with SAH have some degree of regional wall motion abnormality (RWMA) consistent with NSM.[118–121] NSM seemed to occur most commonly within the first 2 days after SAH, and there was a trend toward greater mortality when compared with SAH without RWMA (25 vs 15%, $P = .13$).[118] Other studies have found a similar trend of increased mortality associated with NSM after SAH.[122]

Risk Factors

Risk factors for females with NSM include, poor Hunt Hess grade aneurysmal SAH,[118] young age, posterior circulation aneurysms, poor Fisher grade SAH, and the presence of hydrocephalus.[123] Certain β_1, β_2, and α_2 genetic polymorphisms are also associated with NSM in the setting of SAH.[124] Severe RWMA was associated with increased risk for DCI in at least 1 study.[125] Risk of NSM is even higher in those who develop vasospasm and DCI (39% compared with 13% in the non-NSM group).[124]

Diagnosis and Management

Diagnosis of NSM

Diagnosis of NSM requires a high level of clinical suspicion and exclusion of AMI based on clinical, laboratory, EKG, and echocardiography results (**Table 7**). The diagnosis of NSM requires an inciting psychological or physical stress, which commonly results in dynamic EKG changes, increases in biomarkers of cardiac injury, and reversible dysfunction in LV wall motion, involving multiple coronary vascular territories. In some cases, cardiac catheterization may be necessary to exclude significant coronary artery occlusion. **Fig. 3** outlines the clinical decision tree in differentiating NSM from myocardial infarction (MI).

Table 7
Key clinical and diagnostic features of NSM

Triggering event	Psychological or physical stress
Clinical characteristics	Female predominance AMI or acute coronary syndrome–like presentation, such as chest pain or dyspnea Hemodynamic instability if cardiogenic shock occurs Sudden death
Diagnostic features	No previous history of CAD/CHF Mild increase of cardiac TnI (typically <2.8 ng/mL): increases as early as day 1, peaks ≤3 d; normalizes in 3–8 d Increased BNP (up to >1000 pg/mL, normally <100 pg/mL), as early as day 1 EKG abnormalities: arrhythmias, QT interval prolongation, ST segment elevation/depression, and T-wave inversions in anterior precordial leads New-onset echocardiogram-proven global wall motion abnormality or RWMA not specific to a coronary distribution or systolic or diastolic LV/RV dysfunction Chest radiography: pulmonary edema Negative coronary angiography Complete or partial resolution of cardiac abnormalities on follow-up EKG and echocardiography

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; RV, right ventricle.

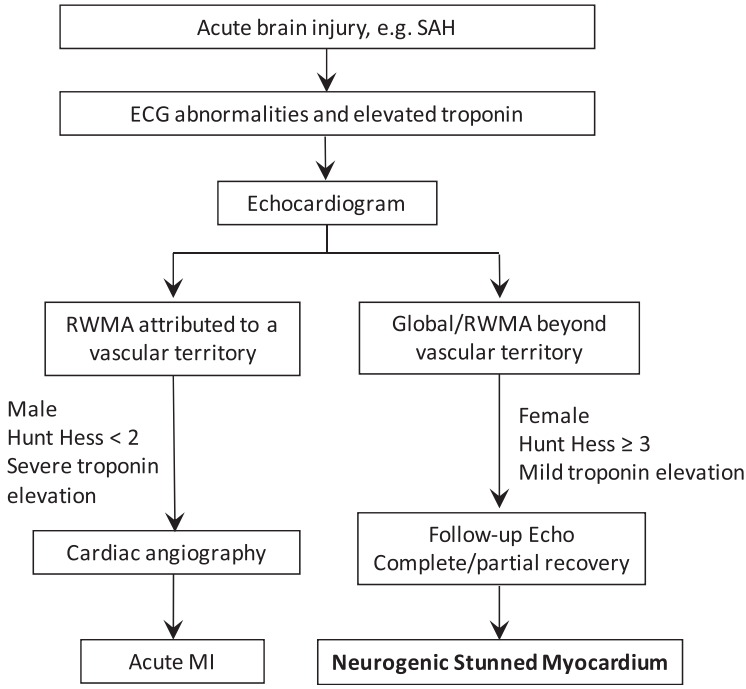


Fig. 3. Steps involved in the diagnosis of NSM.

EKG AND SERUM MARKERS

The association of aneurysmal SAH with EKG and echocardiographic abnormalities has been well noted. EKG changes have been found in 50% to 90% of patients with aneurysmal SAH.[118,126–129] Common EKG abnormalities include arrhythmia and QT interval prolongation, ST segment elevation or depression, and T-wave inversions, which can also be seen with MI.

Levels of TnI, a serum marker of myocardial injury, are increased in 20% to 68% patients after SAH,[109,130,131] with levels peaking by day 2.[130] Peak levels tend to be mild, with 18% to 25% levels of TnI greater than 10.[123,130] Increased TnI levels are commonly seen in the setting of poor Hunt Hess grade, female gender, hypotension, and increased vasopressor requirement and are associated with LV dysfunction, DCI, and death.[123,130,132] Similarly, an increase in B-type natriuretic peptide (BNP) has been associated with RWMA, cardiac dysfunction, pulmonary edema, need for neurointerventional treatment of DCI, and in-hospital mortality.[132,133]

ECHOCARDIOGRAPHY

Recognizing echocardiography changes is critical to identifying NSM. In NSM, dilated apical or midapical LV segments with hypokinesis or akinesis extend beyond a single coronary artery distribution in the absence of coronary artery obstruction. In a prospective study of 300 patients with SAH, RWMA were found in 26%, with 8% having a significant reduction in EF of less than 50%.[134] Reduced EF was associated with reduced blood pressure and greater vasopressor requirement, although whether the vasopressor reduced EF by increasing afterload or was required because of reduced

EF-associated hypotension is unclear.[132] Unlike AMI, echocardiographic changes in NSM are partially or completely reversible in weeks.

COMPLICATIONS CAUSED BY NSM

Although associated with a greater disease severity at SAH presentation, NSM is an independent predictor of death with an OR of 2.71 (95% CI 1.012–7.288).[120] A possible explanation for this finding may be that NSM-related RWMA can result in moderate or severe reduction in LV function, potentially reducing cerebral blood flow, and putting patients at risk for DCI and death.[123] Other less commonly described complications are listed in **Box 10**.[135,136]

MANAGEMENT OF NSM

Management of NSM in the setting of SAH is mainly supportive and relates to the phase of neurologic injury (**Fig. 4**). Initial therapy should be aimed at reducing the inciting neurologic injury whenever possible. Increased ICP should be treated aggressively with hyperosmolar therapy, CSF diversion, and surgical evacuation of hematoma, as necessary. Approximately 3 to 14 days after SAH, the risk for developing DCI is highest. Once DCI develops, treatment consists of intravenous fluid administration and vasopressor administration. This therapy in the setting of reduced LV function may be counterproductive by increasing afterload with vasopressors and preload with fluids, resulting in congestive heart failure, pulmonary edema, and potentially exacerbating cerebral hypoperfusion. By contrast, managing congestive heart failure with diuresis increases the risk for DCI. Administration of inotropes, such as milrinone or dobutamine, with the aid of cardiac output monitoring with a Swan-Ganz catheter can be considered.[137] In more severe cases of LV dysfunction, an intra-aortic balloon pump can be considered.[138,139] Endovascular treatment of DCI, typically reserved for failure of vasopressors and fluids to resolve DCI, may need to be considered sooner in cases of reduced LV function.

NSM is a well-recognized complication of acute brain injury related in part to excessive stress-induced catecholamine release. Patients with NSM present with symptoms, ECG findings, and TnI levels similar to AMI. However, on echocardiogram, regional wall motion abnormalities involve multiple vascular territories and can be moderate to severe in 10% of patients with SAH. Abnormal cardiac function can contribute to DCI and complicate therapy.

Box 10
In-hospital complications of NSM

- Death
- RWMA, heart failure
- Cardiogenic shock
- Atrial fibrillation
- Ventricular arrhythmia
- LV thrombosis
- Severe mitral regurgitation
- LV outflow tract obstruction
- DCI

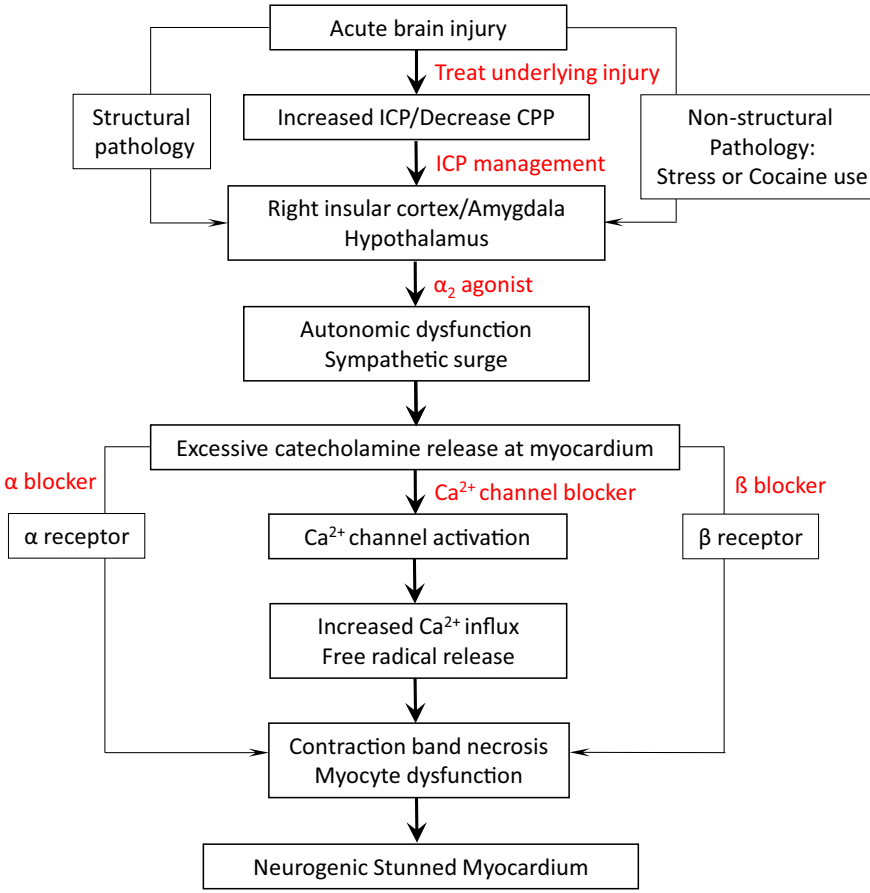


Fig. 4. Management of NSM.

SUMMARY

Cardiac emergencies and cardiovascular procedures can have significant neurologic implications. Both in-hospital and out-of-hospital CA and its neurologic sequelae remain major clinical problems. Recent advances in postresuscitative care, including TH, have improved outcomes after adult CA over the past decade. Data continue to emerge regarding identifying more reliable predictors of neurologic outcomes as well as the optimum strategy for targeted temperature management in the post-CA setting. The management strategy remains controversial for patients with type A aortic dissection who have cerebrovascular involvement, with observational data showing that early surgery may improve survival and reverse some of the neurologic deficits. Stroke and TIAs remain the most common neurologic complications associated with LVAD placement and CABG. Newer LVADs with biointimal surface may reduce the risk of embolic complications. However, management of ICH associated with LVADs remains challenging, with limited data suggesting that withholding aspirin for a week and anticoagulation for 10 days may be safe. There are good data showing that OPCAB is associated with a lower risk of embolic complications, with conflicting data regarding its beneficial effect on long-term cognitive outcomes. IE continues to

be associated with significant neurologic sequelae. Early initiation of antimicrobial treatment significantly decreases the risk of recurrent embolic events. Timing of cardiac surgery remains controversial, with recent data showing that early surgery may be performed safely in selected patients with ischemic strokes. Our understanding of the pathophysiology of NSM and its effects on patient outcomes continues to improve.

REFERENCES

1. Callans DJ. Out-of-hospital cardiac arrest–the solution is shocking. N Engl J Med 2004;351(7):632–4.
2. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the United States. Circulation 2003;107(16):2096–101.
3. Pusswald G, Fertl E, Faltl M, et al. Neurological rehabilitation of severely disabled cardiac arrest survivors. Part II. Life situation of patients and families after treatment. Resuscitation 2000;47(3):241–8.
4. Herlitz J, Andersson E, Bang A, et al. Experiences from treatment of out-of-hospital cardiac arrest during 17 years in Goteborg. Eur Heart J 2000;21(15):1251–8.
5. Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;67(2):203–10.
6. Levy DE, Caronna JJ, Singer BH, et al. Predicting outcome from hypoxic-ischemic coma. JAMA 1985;253(10):1420–6.
7. Zandbergen EG, Hijdra A, Koelman JH, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology 2006;66(1):62–8.
8. Edgren E, Hedstrand U, Kelsey S, et al. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994;343(8905):1055–9.
9. Chen R, Bolton CF, Young B. Prediction of outcome in patients with anoxic coma: a clinical and electrophysiologic study. Crit Care Med 1996;24(4):672–8.
10. Bassetti C, Bomio F, Mathis J, et al. Early prognosis in coma after cardiac arrest: a prospective clinical, electrophysiological, and biochemical study of 60 patients. J Neurol Neurosurg Psychiatry 1996;61(6):610–5.
11. Logi F, Fischer C, Murri L, et al. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 2003;114(9):1615–27.
12. Gendo A, Kramer L, Hafner M, et al. Time-dependency of sensory evoked potentials in comatose cardiac arrest survivors. Intensive Care Med 2001;27(8):1305–11.
13. Fogel W, Krieger D, Veith M, et al. Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. Crit Care Med 1997;25(7):1133–8.
14. Wijdicks EF, Parisi JE, Sharbrough FW. Prognostic value of myoclonus status in comatose survivors of cardiac arrest. Ann Neurol 1994;35(2):239–43.
15. Berek K, Lechleitner P, Luef G, et al. Early determination of neurological outcome after prehospital cardiopulmonary resuscitation. Stroke 1995;26(4):543–9.
16. Edgren E, Hedstrand U, Nordin M, et al. Prediction of outcome after cardiac arrest. Crit Care Med 1987;15(9):820–5.
17. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. Neurology 1988;38(3):401–5.

18. Kano T, Shimoda O, Morioka T, et al. Evaluation of the central nervous function in resuscitated comatose patients by multilevel evoked potentials. Resuscitation 1992;23(3):235–48.
19. Earnest MP, Breckinridge JC, Yarnell PR, et al. Quality of survival after out-of-hospital cardiac arrest: predictive value of early neurologic evaluation. Neurology 1979;29(1):56–60.
20. Fugate JE, Wijdicks EF, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol 2010;68(6):907–14.
21. Al Thenayan E, Savard M, Sharpe M, et al. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology 2008;71(19):1535–7.
22. Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014. [Epub ahead of print].
23. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–63.
24. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549–56.
25. Fugate JE, Moore SA, Knopman DS, et al. Cognitive outcomes of patients undergoing therapeutic hypothermia after cardiac arrest. Neurology 2013;81(1):40–5.
26. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med 2013;369(23):2197–206.
27. Gaul C, Dietrich W, Friedrich I, et al. Neurological symptoms in type A aortic dissections. Stroke 2007;38(2):292–7.
28. Di Eusanio M, Patel HJ, Nienaber CA, et al. Patients with type A acute aortic dissection presenting with major brain injury: should we operate on them? J Thorac Cardiovasc Surg 2013;145(Suppl 3):213–21.e1.
29. Estrera AL, Garami Z, Miller CC, et al. Acute type A aortic dissection complicated by stroke: can immediate repair be performed safely? J Thorac Cardiovasc Surg 2006;132(6):1404–8.
30. Blanco M, Diez-Tejedor E, Larrea JL, et al. Neurologic complications of type I aortic dissection. Acta Neurol Scand 1999;99(4):232–5.
31. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000;283(7):897–903.
32. Lynch DR, Dawson TM, Raps EC, et al. Risk factors for the neurologic complications associated with aortic aneurysms. Arch Neurol 1992;49(3):284–8.
33. Conzelmann LO, Hoffmann I, Blettner M, et al. Analysis of risk factors for neurological dysfunction in patients with acute aortic dissection type A: data from the German Registry for Acute Aortic Dissection type A (GERAADA). Eur J Cardiothorac Surg 2012;42(3):557–65.
34. Wong CS, Healy D, Canning C, et al. A systematic review of spinal cord injury and cerebrospinal fluid drainage after thoracic aortic endografting. J Vasc Surg 2012;56(5):1438–47.
35. Svensson LG, Hess KR, D'Agostino RS, et al. Reduction of neurologic injury after high-risk thoracoabdominal aortic operation. Ann Thorac Surg 1998;66(1):132–8.
36. Coselli JS, LeMaire SA, Köksoy C, et al. Cerebrospinal fluid drainage reduces paraplegia after thoracoabdominal aortic aneurysm repair: results of a randomized clinical trial. J Vasc Surg 2002;35(4):631–9.

37. Reitz BA, Crawford ES, Svensson LG, et al. A prospective randomized study of cerebrospinal fluid drainage to prevent paraplegia after high-risk surgery on the thoracoabdominal aorta. J Vasc Surg 1991;13(1):36–46.
38. Morimoto N, Okada K, Okita Y. Lack of neurologic improvement after aortic repair for acute type A aortic dissection complicated by cerebral malperfusion: predictors and association with survival. J Thorac Cardiovasc Surg 2011;142(6): 1540–4.
39. Czerny M, Fleck T, Zimpfer D, et al. Risk factors of mortality and permanent neurologic injury in patients undergoing ascending aortic and arch repair. J Thorac Cardiovasc Surg 2003;126(5):1296–301.
40. Krähenbühl ES, Immer FF, Stalder M, et al. Temporary neurological dysfunction after surgery of the thoracic aorta: a predictor of poor outcome and impaired quality of life. Eur J Cardiothorac Surg 2008;33(6):1025–9.
41. Kruger T, Weigang E, Hoffmann I, et al. Cerebral protection during surgery for acute aortic dissection type A: results of the German Registry for Acute Aortic Dissection Type A (GERAADA). Circulation 2011;124(4):434–43.
42. Haldenwang PL, Wahlers T, Himmels A, et al. Evaluation of risk factors for transient neurological dysfunction and adverse outcome after repair of acute type A aortic dissection in 122 consecutive patients. Eur J Cardiothorac Surg 2012; 42(5):e115–20.
43. Rylski B, Hoffmann I, Beyersdorf F, et al. Acute aortic dissection type A: age-related management and outcomes reported in the German Registry for Acute Aortic Dissection type A (GERAADA) of over 2000 patients. Ann Surg 2014; 259(3):598–604.
44. Piccione W Jr. Left ventricular assist device implantation: short and long-term surgical complications. J Heart Lung Transplant 2000;19(Suppl 8):S89–94.
45. Nakajima I, Kato TS, Komamura K, et al. Pre- and post-operative risk factors associated with cerebrovascular accidents in patients supported by left ventricular assist device. Circ J 2011;75(5):1138–46.
46. Schmid C, Weyand M, Nabavi DG, et al. Cerebral and systemic embolization during left ventricular support with the Novacor N100 device. Ann Thorac Surg 1998;65(6):1703–10.
47. Popov AF, Hosseini MT, Zych B, et al. Clinical experience with HeartWare left ventricular assist device in patients with end-stage heart failure. Ann Thorac Surg 2012;93(3):810–5.
48. Lazar RM, Shapiro PA, Jaski BE, et al. Neurological events during long-term mechanical circulatory support for heart failure: the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) experience. Circulation 2004;109(20):2423–7.
49. Pae WE, Connell JM, Boehmer JP, et al. Neurologic events with a totally implantable left ventricular assist device: European LionHeart Clinical Utility Baseline Study (CUBS). J Heart Lung Transplant 2007;26(1):1–8.
50. Copeland JG, Copeland H, Gustafson M, et al. Experience with more than 100 total artificial heart implants. J Thorac Cardiovasc Surg 2012;143(3):727–34.
51. Tsukui H, Abla A, Teuteberg JJ, et al. Cerebrovascular accidents in patients with a ventricular assist device. J Thorac Cardiovasc Surg 2007;134(1):114–23.
52. Yuan N, Arnaoutakis GJ, George TJ, et al. The spectrum of complications following left ventricular assist device placement. J Card Surg 2012;27(5): 630–8.
53. Thomas CE, Jichici D, Petrucci R, et al. Neurologic complications of the Novacor left ventricular assist device. Ann Thorac Surg 2001;72(4):1311–5.

54. Dell'Aquila AM, Schneider SR, Schlarb D, et al. Initial clinical experience with the HeartWare left ventricular assist system: a single-center report. Ann Thorac Surg 2013;95(1):170–7.
55. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. N Engl J Med 2014;370(1):33–40.
56. John R, Panch S, Hrabe J, et al. Activation of endothelial and coagulation systems in left ventricular assist device recipients. Ann Thorac Surg 2009;88(4):1171–9.
57. Spanier T, Oz M, Levin H, et al. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. J Thorac Cardiovasc Surg 1996; 112(4):1090–7.
58. Kato TS, Schulze PC, Yang J, et al. Pre-operative and post-operative risk factors associated with neurologic complications in patients with advanced heart failure supported by a left ventricular assist device. J Heart Lung Transplant 2012; 31(1):1–8.
59. Vermes E, Kirsch M, Farrokhi T, et al. Management of intracranial hemorrhage in patients with mechanical circulatory support: a role for low-molecular-weight heparins? ASAIO J 2005;51(4):485–6.
60. Wilson TJ, Stetler WR Jr, Al-Holou WN, et al. Management of intracranial hemorrhage in patients with left ventricular assist devices. J Neurosurg 2013;118(5): 1063–8.
61. Galvez-Acebal J, Rodriguez-Bano J, Martinez-Marcos FJ, et al. Prognostic factors in left-sided endocarditis: results from the Andalusian multicenter cohort. BMC Infect Dis 2010;10:17.
62. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169(5): 463–73.
63. Heiro M, Nikoskelainen J, Engblom E, et al. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med 2000;160(18):2781–7.
64. Sonneville R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. Crit Care Med 2011;39(6):1474–81.
65. Pruitt AA, Rubin RH, Karchmer AW, et al. Neurologic complications of bacterial endocarditis. Medicine (Baltimore) 1978;57(4):329–43.
66. Anderson DJ, Goldstein LB, Wilkinson WE, et al. Stroke location, characterization, severity, and outcome in mitral vs aortic valve endocarditis. Neurology 2003;61(10):1341–6.
67. Vilacosta I, Graupner C, San Roman JA, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002;39(9): 1489–95.
68. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation 2013;127(23):2272–84.
69. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112(1):69–75.
70. Snygg-Martin U, Gustafsson L, Rosengren L, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47(1):23–30.

71. Salgado AV, Furlan AJ, Keys TF, et al. Neurologic complications of endocarditis: a 12-year experience. Neurology 1989;39(2 Pt 1):173–8.
72. Hart RG, Foster JW, Luther MF, et al. Stroke in infective endocarditis. Stroke 1990;21(5):695–700.
73. Horstkotte D, Follath F, Gutschik E, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European Society of Cardiology. Eur Heart J 2004;25(3):267–76.
74. Thuny F, Avierinos JF, Tribouilloy C, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J 2007;28(9):1155–61.
75. Mourvillier B, Trouillet JL, Timsit JF, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. Intensive Care Med 2004;30(11):2046–52.
76. Peters PJ, Harrison T, Lennox JL. A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis. Lancet Infect Dis 2006; 6(11):742–8.
77. Dickerman SA, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J 2007; 154(6):1086–94.
78. Netzer RO, Zollinger E, Seiler C, et al. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. Heart 2000; 84(1):25–30.
79. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med 2001;345(18):1318–30.
80. Hoen B, Alla F, Selton-Suty C, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002;288(1):75–81.
81. Beynon RP, Bahl VK, Prendergast BD. Infective endocarditis. BMJ 2006; 333(7563):334–9.
82. Gillinov AM, Shah RV, Curtis WE, et al. Valve replacement in patients with endocarditis and acute neurologic deficit. Ann Thorac Surg 1996;61(4):1125–9 [discussion: 1130].
83. Maruyama M, Kuriyama Y, Sawada T, et al. Brain damage after open heart surgery in patients with acute cardioembolic stroke. Stroke 1989;20(10): 1305–10.
84. Eishi K, Kawazoe K, Kuriyama Y, et al. Surgical management of infective endocarditis associated with cerebral complications. Multi-center retrospective study in Japan. J Thorac Cardiovasc Surg 1995;110(6):1745–55.
85. Piper C, Wiemer M, Schulte HD, et al. Stroke is not a contraindication for urgent valve replacement in acute infective endocarditis. J Heart Valve Dis 2001;10(6): 703–11.
86. Barsic B, Dickerman S, Krajinovic V, et al. Influence of the timing of cardiac surgery on the outcome of patients with infective endocarditis and stroke. Clin Infect Dis 2013;56(2):209–17.
87. Habib G, Hoen B, Tornos P, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30(19):2369–413.

88. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111(23):e394–434.
89. Angstwurm K, Borges AC, Halle E, et al. Timing the valve replacement in infective endocarditis involving the brain. J Neurol 2004;251(10):1220–6.
90. Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 1996;335(25):1857–63.
91. Mickleborough LL, Walker PM, Takagi Y, et al. Risk factors for stroke in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 1996; 112(5):1250–8 [discussion: 1258–9].
92. Redmond JM, Greene PS, Goldsborough MA, et al. Neurologic injury in cardiac surgical patients with a history of stroke. Ann Thorac Surg 1996;61(1):42–7.
93. Puskas JD, Winston AD, Wright CE, et al. Stroke after coronary artery operation: incidence, correlates, outcome, and cost. Ann Thorac Surg 2000;69(4):1053–6.
94. Wolman RL, Nussmeier NA, Aggarwal A, et al. Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. Stroke 1999;30(3): 514–22.
95. McKhann GM, Goldsborough MA, Borowicz LM Jr, et al. Predictors of stroke risk in coronary artery bypass patients. Ann Thorac Surg 1997;63(2):516–21.
96. Kapetanakis EI, Stamou SC, Dullum MK, et al. The impact of aortic manipulation on neurologic outcomes after coronary artery bypass surgery: a risk-adjusted study. Ann Thorac Surg 2004;78(5):1564–71.
97. Bucerius J, Gummert JF, Borger MA, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2003; 75(2):472–8.
98. Likosky DS, Leavitt BJ, Marrin CAS, et al. Intra- and postoperative predictors of stroke after coronary artery bypass grafting. Ann Thorac Surg 2003;76(2): 428–34.
99. Bucerius J, Gummert JF, Borger MA, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 2004;127(1):57–64.
100. Cleveland JC Jr, Shroyer AL, Chen AY, et al. Off-pump coronary artery bypass grafting decreases risk-adjusted mortality and morbidity. Ann Thorac Surg 2001;72(4):1282–8 [discussion: 1288–9].
101. Stamou SC, Jablonski KA, Pfister AJ, et al. Stroke after conventional versus minimally invasive coronary artery bypass. Ann Thorac Surg 2002;74(2):394–9.
102. Patel NC, Grayson AD, Jackson M, et al. The effect off-pump coronary artery bypass surgery on in-hospital mortality and morbidity. Eur J Cardiothorac Surg 2002;22(2):255–60.
103. Motallebzadeh R, Bland JM, Markus HS, et al. Neurocognitive function and cerebral emboli: randomized study of on-pump versus off-pump coronary artery bypass surgery. Ann Thorac Surg 2007;83(2):475–82.
104. Stroobant N, Van Nooten G, Van Belleghem Y, et al. Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. Chest 2005;127(6):1967–76.

105. Diegeler A, Borgermann J, Kappert U, et al. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. N Engl J Med 2013;368(13):1189–98.
106. Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012;366(16):1489–97.
107. Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med 2013;368(13):1179–88.
108. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. N Engl J Med 2009;361(19):1827–37.
109. Tung P, Kopelnik A, Banki N, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. Stroke 2004;35(2):548–51.
110. Porto I, Della Bona R, Leo A, et al. Stress cardiomyopathy (tako-tsubo) triggered by nervous system diseases: a systematic review of the reported cases. Int J Cardiol 2013;167(6):2441–8.
111. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113(14):1807–16.
112. Nguyen H, Zaroff JG. Neurogenic stunned myocardium. Curr Neurol Neurosci Rep 2009;9(6):486–91.
113. Cheung RT, Hachinski V. The insula and cerebrogenic sudden death. Arch Neurol 2000;57(12):1685–8.
114. Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke 2002;33(6):1671–6.
115. Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. Physiol Rev 1999;79(2):609–34.
116. Lee VH, JK O, SL M, et al. Mechanisms in neurogenic stress cardiomyopathy after aneurysmal subarachnoid hemorrhage. Neurocrit Care 2006;5(3):243–9.
117. Previtali M, Repetto A, Panigada S, et al. Left ventricular apical ballooning syndrome: prevalence, clinical characteristics and pathogenetic mechanisms in a European population. Int J Cardiol 2009;134(1):91–6.
118. Banki N, Kopelnik A, Tung P, et al. Prospective analysis of prevalence, distribution, and rate of recovery of left ventricular systolic function in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 2006;105(1):15–20.
119. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation 2008;118(4):397–409.
120. Lee VH, Connolly HM, Fulgham JR, et al. Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction. J Neurosurg 2006;105(2):264–70.
121. Donaldson JW, Pritz MB. Myocardial stunning secondary to aneurysmal subarachnoid hemorrhage. Surg Neurol 2001;55(1):12–6 [discussion: 16].
122. Kilbourn KJ, Levy S, Staff I, et al. Clinical characteristics and outcomes of neurogenic stress cardiomyopathy in aneurysmal subarachnoid hemorrhage. Clin Neurol Neurosurg 2013;115(7):909–14.
123. Temes RE, Tessitore E, Schmidt JM, et al. Left ventricular dysfunction and cerebral infarction from vasospasm after subarachnoid hemorrhage. Neurocrit Care 2010;13(3):359–65.

124. Zaroff JG, Pawlikowska L, Miss JC, et al. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. Stroke 2006;37(7):1680–5.
125. Mayer SA, Lin J, Homma S, et al. Myocardial injury and left ventricular performance after subarachnoid hemorrhage. Stroke 1999;30(4):780–6.
126. Sakr YL, Lim N, Amaral AC, et al. Relation of ECG changes to neurological outcome in patients with aneurysmal subarachnoid hemorrhage. Int J Cardiol 2004;96(3):369–73.
127. Lanzino G, Kongable GL, Kassell NF. Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. J Neurosurg Anesthesiol 1994;6(3):156–62.
128. Davies KR, Gelb AW, Manninen PH, et al. Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities. Br J Anaesth 1991;67(1):58–63.
129. Brouwers PJ, Wijdicks EF, Hasan D, et al. Serial electrocardiographic recording in aneurysmal subarachnoid hemorrhage. Stroke 1989;20(9):1162–7.
130. Naidech AM, Kreiter KT, Janjua N, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. Circulation 2005;112(18):2851–6.
131. Horowitz MB, Willet D, Keffer J. The use of cardiac troponin-I (cTnI) to determine the incidence of myocardial ischemia and injury in patients with aneurysmal and presumed aneurysmal subarachnoid hemorrhage. Acta Neurochir (Wien) 1998;140(1):87–93.
132. Yarlagadda S, Rajendran P, Miss JC, et al. Cardiovascular predictors of inpatient mortality after subarachnoid hemorrhage. Neurocrit Care 2006;5(2):102–7.
133. Tung PP, Olmsted E, Kopelnik A, et al. Plasma B-type natriuretic peptide levels are associated with early cardiac dysfunction after subarachnoid hemorrhage. Stroke 2005;36(7):1567–9.
134. Kothavale A, Banki NM, Kopelnik A, et al. Predictors of left ventricular regional wall motion abnormalities after subarachnoid hemorrhage. Neurocrit Care 2006;4(3):199–205.
135. Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of takotsubo cardiomyopathy and long-term prognosis. Herz 2010;35(4):240–3.
136. Brenner R, Weilenmann D, Maeder MT, et al. Clinical characteristics, sex hormones, and long-term follow-up in Swiss postmenopausal women presenting with takotsubo cardiomyopathy. Clin Cardiol 2012;35(6):340–7.
137. Naidech A, Du Y, Kreiter KT, et al. Dobutamine versus milrinone after subarachnoid hemorrhage. Neurosurgery 2005;56(1):21–61 [discussion: 26–7].
138. Lazaridis C, Pradilla G, Nyquist PA, et al. Intra-aortic balloon pump counterpulsation in the setting of subarachnoid hemorrhage, cerebral vasospasm, and neurogenic stress cardiomyopathy. Case report and review of the literature. Neurocrit Care 2010;13(1):101–8.
139. Apostolides PJ, Greene KA, Zabramski JM, et al. Intra-aortic balloon pump counterpulsation in the management of concomitant cerebral vasospasm and cardiac failure after subarachnoid hemorrhage: technical case report. Neurosurgery 1996;38(5):1056–9 [discussion: 1059–60].